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# Immunoadsorption Therapy (Therasorb) in Patients with Severe Lupus Erythematosus

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**Schlüsselwörter:** Systemischer Lupus erythematosus – Plasmapherese – Immunadsorption.

**Summary:** Therapeutic removal of immune complexes and antibodies by plasmapheresis has been used in patients with systemic lupus erythematosus (SLE) since 1974. Modern methods of selective adsorption of immunoglobulins from the patient plasma (immunoadsorption, IAS) have been developed; they deserve to be investigated as a tool in the management of difficult cases of SLE.

We report our experience in an uncontrolled series of five consecutive SLE patients, in whom cytotoxic immunosuppression was contraindicated or not sufficient to control the disease. Ig-Therasorb columns containing polyclonal sheep antihuman immunoglobulin antibodies were used for IAS for periods of 4 to 54 weeks. In order to prevent rebound autoantibody production, low doses of normal human immunoglobulin were substituted.

Improvement in clinical and laboratory signs of disease activity was observed in all patients. In two patients the effect of cyclophosphamide therapy for lupus pneumonitis and lupus-associated thrombopenic purpura was consolidated. In three patients suffering from pancytopenia or lupus vasculitis, the use of cytotoxic substances could be avoided for more than a year.

IAS seems to be a safe replacement of conventional plasmapheresis in difficult cases of severe lupus complications. Although controlled studies are lacking, this method may occupy a few important niches as an adjunct in managing immune complex mediated diseases.

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## Immunadsorptionstherapie bei Patienten mit schwerem Verlauf von systemischem Lupus erythematosus

**Zusammenfassung:** Bei schweren Verlaufsformen der Autoimmunerkrankung Systemischer Lupus Erythematosus (SLE) wurde die Plasmapheresetherapie wegen der langfristig erhöhten Infektionsneigung und dem negativen Ergebnis von kontrollierten Wirksamkeitsstudien verlassen. Die Immunadsorption (IAS) mit Immunglobulin-bindenden Substraten erlaubt eine spezifischere Entfernung der als pathogen angesehenen Autoantikörper und könnte eine Bereicherung beim Management von SLE-Patientinnen mit hoher Krankheitsaktivität trotz konventioneller immunsuppressiver Therapie sein.

Wir beschreiben den Erfolg einer Immunadsorptionsbehandlung bei Patientinnen mit aktivem SLE, bei denen eine Zyklophosphamidtherapie nicht ausreichend oder kontraindiziert erschien. Separiertes Patientenplasma wurde mit polyklonalen Schafantikörpern gegen humanes Immunglobulin (Ig-Therasorb-Säulen) adsorbiert, nach jeweils drei Immunglobulinapheresen wurde je 15 g Immunglobulin von gesunden Spendern substituiert.

Bei allen fünf Patienten kam es zu einer raschen Besserung der klinischen und serologischen Symptomatik. Bei zwei Patientinnen wurde der Erfolg einer initialen Zyklophosphamidtherapie nach Lupuspneumonitis und Lupus-assoziiierter thrombopenischer Purpura konsolidiert, bei drei Patientinnen

mit Pancytopenie oder Lupusvasculitis konnte die Verwendung von zytotoxischen Substanzen temporär vermieden werden. Die Immunadsorption stellt einen Ersatz für die konventionelle Plasmapherese dar und erscheint bei SLE mit schwierigem Krankheitsverlauf als wichtige Zusatzmöglichkeit zur immunsuppressiven Therapie. Der exakte Stellenwert dieser aufwendigen Behandlungsform muss aber in kontrollierten Studien ermittelt werden.

## Background

The pathophysiology of systemic lupus erythematosus (SLE) is characterized by the production of a variety of autoantibodies and an impaired clearance of circulating immune complexes.

In severe cases of SLE the removal of plasma constituents has been advocated, when the administration of corticosteroids and cytotoxic drugs is not sufficient to control serious organ damage (4, 12, 28, 31). Moreover, long-term use of plasmapheresis in conjunction with high-dose cyclophosphamide has been suggested (7, 8). However, the side effects associated with plasmapheresis (1) and the lack of superiority of plasmapheresis/cyclophosphamide when compared to cyclophosphamide treatment alone (17, 18, 29) have led to the abandonment of plasma removal in the management of SLE in many centres.

Nonetheless, life-threatening bouts of SLE activity or situations where the use of cytotoxic drugs is contraindicated still make the clinician aware of the need for more effective therapeutic intervention. The concept of removing pathogenic immunoglobulins has thus been further pursued by using advanced technologies that allow removal of the culprit molecules in a more specific manner. Using several different technologies, selective immunoadsorption of immunoglobu-

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lins (immunoglobulin-apheresis, IAS) was applied successfully in single cases or uncontrolled series of SLE patients (11, 14, 22, 23, 24, 25). Here we report the retrospective outcome analysis of five patients who were treated with immunoglobulin apheresis and subsequent low-dose immunoglobulin substitution.

## Patients and methods

For a period of 1 year, five patients with active SLE were admitted to our apheresis unit. The purpose of IAS was to avoid further cytotoxic treatment in patients who had either experienced severe adverse reactions (including bone marrow depression) or who expressed concerns about the detrimental effects on ovarian function. All patients gave informed consent to the application of the therapeutic modality of IAS.

For Ig-apheresis (IAS) blood was drawn continuously from an antecubital vein via a 15-gauge dialysis needle at a flow rate of 50 to 80 ml/min. Coagulation was prevented with heparin (input rate of 20 units/min; not exceeding 5000 units each treatment) and citrate as ACD-A (anticoagulant citrate dextrose, formula A, Baxter, Munich, Germany). The ratio of citrate to whole blood flow was kept at 1:22 (5).

For primary plasma separation, an autopheresis-Ctm TPS (Therapeutic Plasma System, Baxter, Deerfield, IL, USA) was employed. The functional separation unit of the device is the Plasmacell-CR, a rotating cylindrical membrane housed in a plastic casing. The Plasmacell-CR is capable of fast and highly efficient plasma separation using a small membrane surface area (70 cm<sup>2</sup>) with a blood processing volume of only 7 ml. IAS was performed in an automated double-needle, continuous flow operation in which the TPS is connected with an adsorption-desorption-automate (ADA; Baxter, Munich, Germany) controlling the flow of plasma and regeneration solutions.

For IgG immunoadsorption, two columns are used each containing 150 ml Sepharose coupled with polyclonal sheep antibodies binding human IgG heavy and light chains (Ig-Therasorb, Baxter, Munich, Germany). Each column has an immunoglobulin-binding capacity of approximately 1.2 to 1.4 g. In each adsorption cycle (lasting about 15 min) 400 ml of plasma are loaded on one column with a plasma flow rate

of 20 to 35 ml/min. This system uses two columns, one of which is loading while the other one is desorbing by protein elution with glycine buffer at pH 2.8, followed by washing cycles with phosphate-buffered saline and isotonic sodium chloride solution. A total number of 18 cycles was performed during each immunoadsorption session (mean plasma desorbed 7800 ml). Serum immunoglobulin G levels were reduced to ranges between 200 and 500 mg/dl by IAS performed on two to three consecutive days. Subsequently 10 to 15 g of intravenous immunoglobulin were substituted because we were concerned about a possible rebound of autoantibody production without concomitant immunosuppressive therapy. For long-term application of IAS, this regimen was repeated every 3 weeks for varying periods (see table).

## Patient 1

A 45-year-old woman had been suffering from SLE for 15 years. At the beginning of her disease she had been severely affected by pneumonitis and CNS lupus with organic brain syndrome. During the subsequent years interstitial nephritis and vasculitic purpura on the legs, arms, and trunk developed and she was diagnosed as having an overlap between SLE and primary Sjogren's syndrome. During the 15-year course of her disease she had been treated with a total of 45 g of intravenous cyclophosphamide. She experienced serious adverse effects of immunosuppression (pneumonia, ovarian cancer, herpes zoster). When she developed massive gastrointestinal bleeding due to severe intestinal vasculitis, she received two infusions with 1 g of cyclophosphamide. Concomitantly she was started on the IAS schedule, because we wanted to avoid further cyclophosphamide treatment, which the patient also declined. We observed a rapid clearing of the vasculitic skin rash and colonoscopy showed the disappearance of mucosal bleeding after 1 week. Due to the repeated and reliable improvement of vasculitic purpura on both legs after every IAS treatment, we performed 45 IAS procedures for a period of more than 1 year. It must be mentioned that the skin purpura recurred each time 3 weeks after the IAS procedure despite normal IgG serum levels. No immunosuppressive treatment other than oral prednisolone (5 to 10 mg/d) was given; the patient had no other signs of disease activity and experienced a good quality of life during this

*Table 1. Clinical parameters for five female patients undergoing immunoadsorption therapy (IAS). The description as remission or partial remission does not follow any predefined criteria, but merely depicts the clinically relevant disease activity from the viewpoint of independent physician observers in the outpatient department of our lupus clinic.*

Pat. No.	Reason for IAS	ECLAM	Initial CX	No. of IAS	IVIG	Duration of IAS	ECLAM after IAS	Outcome
1	Gastrointestinal bleeding due to vasculitis – pat. declined further CX	NA	2 × 1 g	45	9 × 15 g	410 days	NA	Gastrointestinal bleeding due to vasculitis – CX reinstituted, died from septicemia
2	Pneumonitis, carditis, adjunctive IAS	6	2 × 1 g	7	7 × 15 g	34 days	2.5	Remission, subsequent GN, azathioprine
3	Haemolytic anaemia, severe leucopenia	6.5	None	7	3 × 10 g	32 days	2.5	RBC, WBC stabilized
4	CNS involvement, thrombopenia, pat. declined further CX	8.5	2 × 1 g	15	7 × 20 g	89 days	1.5	Remission
5	Pancytopenia	4.5	None	15	7 × 15 g	79 days	3	Partial remission

CX = cyclophosphamide; IVIG = intravenous human immunoglobulin substitution; ECLAM = European Consensus Lupus Activity Measurement; RBC = red blood cell count; WBC = white blood cell count

year. Eventually, severe vasculitic colitis with rectal bleeding recurred, fever and thrombopenia as well as high anti-DNA titres and hypocomplementaemia indicated an exacerbation of SLE. Cyclophosphamide was reinstituted and apheresis was terminated. The patient died 1 year later from septicaemia.

#### Patient 2

A 23-year-old lupus patient suffered from progressive respiratory failure requiring intubation and assisted ventilation. Chest x-ray showed massive bilateral nodular alveolar infiltrates. In her previous history, SLE with a malar rash, arthritis, mild proteinuria and high titre antinuclear antibodies had been known for 4 years while she had been treated with azathioprine and low-dose steroids. An open lung biopsy revealed the histological diagnosis of severe acute lupus pneumonitis. An echocardiography showed severely impaired left ventricular function and a pericardial effusion; ECG changes compatible with myocarditis were present. Since high doses of methylprednisolone and cyclophosphamide had no obvious effect for 1 week, adjunctive IAS was performed and after 2 weeks improvement of cardiorespiratory function was noted. In order to consolidate the effect of the initial treatment, seven sessions of IAS was performed for 34 days, after which she was discharged in complete remission. Three months later, an increasing proteinuria (1 g/d) was noted and a kidney biopsy showed a diffuse proliferative glomerulonephritis (WHO Type IV); a conventional treatment regimen with prednisolone, azathioprine and lisinopril was instituted.

#### Patient 3

A 24-year-old female had been suffering for 18 months from SLE with seizures, arthritis, fever, and polyserositis. She was treated with corticosteroids, azathioprine, and cyclosporine. After consultation with a homeopathy-oriented physician, she stopped all allopathic medication and had to be admitted 2 weeks later because of fever, arthritis, fatigue, highly elevated anti-DNA antibodies, haemolytic anaemia, and a white blood cell count of 0.6 G/l. A bone marrow aspirate showed a markedly decreased myelopoiesis. In addition to the administration of high-dose corticosteroids and granulocyte-colony stimulating factor, IAS was performed for a period of 1 month. Clinical symptoms improved and leucocyte counts increased after 2 weeks (peak 2.5 G/l) and there was a stable course of disease without subjective complaints and leucocytes of 1.7 to 3.0 G/l while she was taking 5 mg prednisone daily for 1 year.

#### Patient 4

A 20-year-old woman developed a diffuse maculopapular rash, fever, fatigue and arthralgias. When leucopenia, anaemia, thrombocytopenia, and proteinuria were noted, she was treated with high-dose prednisolone and a cyclophosphamide bolus (800 mg). Eight days later, the patient had a grand mal-seizure and she developed a malar rash, arthritis and polyserositis (pleurisy, pericarditis). In addition, high titre ANA, elevated anti-DNA antibodies and low complement were found and a second cyclophosphamide-bolus (1 g) was administered. Because of the dramatic disease activity and the lack of a short time response to the therapies administered, concomitant treatment with IAS was started. The patient declined further medication with cyclophosphamide because she was concerned of its effects on the ovaries. IAS proce-

dures were continued for 3 months. Six months after the diagnosis of SLE, the patient felt well; without any treatment other than 5 mg of prednisolone she had normal laboratory results except a slight proteinuria (500 mg/d) and an ANA titre of 1:320. A year later, the patient elected to have a pregnancy interrupted for nonmedical reasons.

#### Patient 5

In a 26-year-old woman with incapacitating arthralgia, fever, lymphadenopathy, fatigue, antibodies against dsDNA, Ro/SSA and La/SSB, the symptoms were not sufficiently controlled with steroid treatment; 6 weeks after the institution of oral azathioprine, the patient developed Coombs-positive haemolytic anaemia, thrombocytopenia, and severe leucopenia. Bone marrow aspiration showed a drastically reduced erythro-, myelo- and thrombopoiesis, which were attributed to the previous cytotoxic treatment. After cessation of azathioprine, severe haemolytic anaemia persisted, multiple blood transfusions were necessary and the patient was transferred to our hospital. Upon admission, polyarthritis, a butterfly rash, high titres of anti-DNA and a haemoglobin of 8 g/l were noted. A second bone marrow biopsy showed slight hypocellularity, but an otherwise normal result. The platelet count was 59,000, antibodies to glycoproteins were attached to the platelets. Since high dose steroid administration had been unsuccessful and the patient declined the use of cytotoxic immunosuppressives, we performed IAS for a period of 3 months, the total amount of intravenous immunoglobulin administered during that period was 135 grams. Haemoglobin levels and platelet counts were stabilized at low levels (average 10 g/l Hb and 90,000 thrombocytes). Blood transfusions were no longer necessary and the patient had no subjective symptoms other than alopecia. However, a daily intake of 37.5 mg of prednisolone was necessary during this period, so that IAS was finally terminated. The patient has been at a stable disease activity level since with 20 mg of oral methotrexate per week and 10 mg prednisolone per day.

#### Discussion

Very active SLE can sometimes not be sufficiently controlled by high-dose corticosteroids and cytotoxic drugs. In such desperate disease activity as well as in situations when the use of cytotoxic immunosuppression is undesirable, the request for additional immunotherapy arises. Apheresis has been introduced as an adjunct in the management of this disorder; however, controlled studies of its effectiveness in acute disease exacerbations are not available. While a number of case reports about the successful use of plasmapheresis in acute SLE exist in the literature (6, 10, 19, 22), no benefit could be found when plasmapheresis was compared to cytotoxic treatment alone in controlled studies of lupus nephritis (18, 29). The technical disadvantages of removing whole plasma, namely the need for the substitution of plasma constituents and the lack of specificity in the components removed, are overcome by using immunoglobulin-specific adsorption devices including anti-human IgG, hydrophobic amino acids, protein-A and Clq (3, 11, 13, 15). Individual cases and small series of IAS applications in SLE have been published (11, 14, 20, 21, 22, 23, 24, 25, 26).

What can we learn from the cases presented in this report? Firstly, the procedure of IAS using the Therasorb column was well tolerated by the patients in terms of haemodynamic tol-

erance and the lack of other side effects. Secondly, no valid judgement about the effectiveness of the method can be obtained after we treated a very heterogeneous cohort of SLE patients without predefined outcome parameters. Although in every single case a strongly positive 'impression' about the treatment success developed in our team, a critical evaluation is hampered by the concomitant initial use of cyclophosphamide in some patients and by the fact that we used immunoglobulin substitution. Even relatively small amounts of immunoglobulin from healthy donors might be immunomodulatory by itself, far beyond preventing a hypothetical rebound synthesis of autologous immunoglobulin (2, 16, 30). Moreover, the natural course of SLE as a remitting and relapsing disease makes the evaluation of the very heterogeneous symptoms problematic even in controlled studies.

One open question is the value of IAS as an additional tool in the treatment of critical organ failure in SLE (like in our patient 2): due to rare incidence and the multimorbidity of such patients, and the fact that several therapeutic options are being used simultaneously, controlled studies are unlikely to ever be performed despite the increasing number of positive experiences with apheresis techniques as described extensively by Euler (9).

The other, more pertaining issue is the possible benefit of apheresis and particularly of immunoadsorption instead of cytotoxic immunosuppression in SLE. As in the majority of the patients described in this report, bone marrow toxicity or preceding malignancies and severe infections can preclude the use of the standard drug cyclophosphamide for longer periods of time – is apheresis effective in such rare circumstances? Controlled and prospective investigations may be feasible in cooperative multicentre studies with stringent inclusion criteria (e.g. restricted to certain forms of lupus nephritis, paediatric lupus, or lupus pregnancies) and predefined intervention strategies and follow-up criteria. Until such studies are performed, the use of cost-intensive therapies like IAS is not to be called evidence based.

Nevertheless, immunoadsorption may be seen as a valuable tool in the management of complicated SLE (27).

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## **Plasmapheresis: an adjunct therapy in severe progressive neuropsychiatric lupus.**

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**OBJECTIVE:** We report our experience with use of plasmapheresis (PP) as an adjunct therapy in severe progressive neuropsychiatric systemic lupus erythematosus (NPSLE). **METHOD:** Three patients of NPSLE (including 2 with status epilepticus) who were progressively worsening on steroids or combination of pulse cyclophosphamide (CPM) and steroids were treated with PP followed by synchronized CPM. Pre and post treatment SLE Disease Activity Index (SLEDAI) and laboratory tests were carried out. **RESULTS:** Significant clinical improvement with decrease in SLEDAI occurred immediately following PP. Mean SLEDAI before and after PP were 33 and 11. Mean erythrocyte sedimentation rate decreased from 121 to 31. Rebound flare of disease activity noted in two patients between 7th-10th day requiring additional immunosuppressants or steroids. **CONCLUSIONS:** PP used as an adjunct therapy in severe, progressive NPSLE is well tolerated and can turn the patient around. PP should be followed by synchronized pulse CPM to prevent disease flare.

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